Remarks

Claim 1 is pending. Claim 9 is canceled. Claims 2-4, and 10-11 are canceled. Claims 5-8 were previously withdrawn.

Claim 1 was rejected under 35 USC 103(a) as unpatentable over Pugsley, et al., and Gehrmann, et al., in view of Knobloch, in further view of Rotolo. Applicants respectfully maintain that the invention claimed in Claim 1, which provides an electrophysiology profile of a compound, to determine the extent of significant off-target activity of the compound, without the need for an invasive cardiac electrophysiologic method, by measuring one or more of the arterial refractory period, ventricular refractory period and AV nodal refractory period, and one or more intervals including an electrocardiogram interval and a cardiac electrogram conduction interval, is not obvious in view of the cited references.

In the claimed invention, a Kv1.5 antagonist compound is administered into the cannulated left femoral artery, and a catheter is inserted into the left femoral artery to measure blood pressure. A third catheter, inserted into the right femoral vein, is used to administer ketamine:xylazine. A fourth recording and stimulating catheter is inserted into the right jugular vein and advanced to the near right atrium. A fifth recording and stimulating catheter is inserted into the common carotid of the rat. Two electrodes are used to obtain bipolar ventricular and His bundle electrograms, and two are used to pace the ventricle. Needle electrodes are subcutaneously placed at the right axillary and left inguinal areas of the rat.

In Example 3, applicants assessment of the claimed method using calcium channel antagonists demonstrated that amlodipine resulted in no change in heart rate and no change in AV nodal conduction or AV nodal refractoriness. Diltiazem, in contrast, resulted in significant decrease in heart rate and significant increases in AV nodal conduction and AV nodal refractoriness.

The Examiner concluded on page 10 of the above-referenced office action that it would have been obvious to a person having ordinary skill in the art, from the teachings of Pugsley, et al., Gehrmann, et al., and Knobloch, to determine in vivo cardiac electrophysiology profiles of a compound affecting a cardiac ion channel, such as a potassium channel, including Kv1.5, in rat, upon administration of the compound and simultaneous measurement of atrial refractory period and electrocardiogram interval.

Before discussing Pugsley, et al., Gehrmann, et al., and Knobloch, applicants respectfully point out that one could not determine the cardiac electrophysiology profile of the calcium channel blocker amlodipine, a compound which affects a cardiac ion channel, using the claimed method. Thus, while the Examiner stated it would be obvious to use the claimed

method to determine the electrophysiologic profile of a compound affecting a cardiac ion channel, in fact applicants have found that the method is useful for compounds affecting the Kv1.5 potassium channel but not compounds such as those effecting the calcium ion channel.

Pugsley, et al., describe a method for evaluating actions, on the cardiovascular system and on the myocardial ionic currents in rats, of the selective kappa receptor agonist spiradoline. Drug is administered into the cannulated right jugular vein, and blood pressure effects are measured and recorded in the cannulated left carotid artery. Electrical stimulation of the left ventricle was accomplished via insertion through the chest wall of 2 Teflon coated silver wire stimulating electrodes into the left ventricle.

Applicants respectfully maintain that the claimed procedure differs from the one described by Pugsley, et al. to provide significant off-target activity information. Puglsley, et al., administer drug and measure blood pressure in vessels that are distinct from those used by the present invention. Additionally, Pugsley, et al., do not administer recording and stimulating catheters into the right jugular vein and common carotid of the rat. Pugsley, et al., do not suggest different vessels for administration of drug and measurement of blood pressure. Accordingly, the claimed procedure would not be obvious a person having ordinary skill in the art in view of Pugsley, et al.

Furthermore, Pugsley, et al., in combination with Gehrmann, et al., and Knobloch, and further in view of Rotolo, would not make the claimed invention obvious.

Gehrmann, et al., describe electrophysiologic studies in genetically engineered mice. In the epicardial study, wires are placed on the right ventrical, left ventrical, and right atrium. In the intracardial study, a catheter is advanced from the right internal jugular vein through the right atrium to the right ventrical. Knobloch describes a study of a selective human cardiac ultrarapid delayed rectifier potassium current blockers in pigs.

Rotolo describes an electrocardiography electrode positioning wearable sling device having a plurality of electrocardiographic recording electrodes positioned in contact with predetermined bust areas. Applicants maintain the described sling device provides no direction for assessing the cardiac electrophysiology profile of a Kv1.5 antagonist by simultaneously measuring one or more periods selected from the group consisting of the atrial refractory period, the ventricular refractory period, and the AV nodal refractory period, and one or more intervals selected from an electrocardiogram interval and a cardiac electrogram conduction interval.

Reconsideration and withdrawal of the rejection of Claim 1 under 35 USC

103(a) is respectfully requested.

Respectfully submitted,

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